CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074612

Trade Name : NICOTINE TRANSDERMAL SYSTEM USP 21 MG/DAY

Generic Name: Nicotine Transdermal System USP 21 mg/day
Sponsor : Sano Corporation

Approval Date: October 20, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074612

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074612

APPROVAL LETTER

ANDAs 74-611 (14 mg/day)
74-612 (21 mg/day)
74-645 (7 mg/day)

OCT 20 1997

Sano Corporation
Attention: Diane Servello
3250 Commerce Parkway
Miramar, FL 33025

Dear Madam:

This is in reference to your abbreviated new drug applications dated January 20, 1995 (74-611 and 74-612), and March 9, 1995 (74-645), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nicotine Transdermal System, USP.

Reference is also made to your amendments submitted to each application dated July 31, 1996; April 25, May 9, July 15, August 29, September 2, and October 16, 1997. We also acknowledge your amendments dated April 21, April 25, and May 19, 1995; August 19, 1996; and June 4, June 18, June 19, July 2, and July 3, 1997 submitted to ANDA 74-612.

The listed drug product referenced in your applications is subject to periods of patent protection which expire on May 21, 2008, (patent 5,016,652) and January 23, 2005 (patent 4,597,961). Your applications contain Paragraph IV certifications to each patent under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(4)(B)(iii) of the Act provides that "approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received." You have notified FDA that Sano has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Sano within the statutory forty-five day period.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Nicotine Transdermal System, 7 mg/day, 14 mg/day, and 21 mg/day to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Habitrol 7 mg/day, 14 mg/day, and 21 mg/day, respectively, of Novartis Consumer Health, Inc.). Your drug release testing should be incorporated into the

stability and quality control programs using the same methods proposed in your applications.

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the changes may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours.

10/20/97

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074612

FINAL PRINTED LABELING

NICOTINE TRANSDERMAL SYSTEM 21 mg/day

PRIMARY CONTAINER

FRONT

Nicotine Transdermal System

21 mg/day

FOR TRANSDERMAL USE ONLY

DO NOT USE IF SEAL ON POUCH IS BROKEN

WARNING: KEEP OUT OF REACH OF CHILDREN.

ZL001 09/95

One 29 cm² system which contains 47.3 mg of nicotine.

***Caution:** Federal law prohibits dispensing without prescription.*

[redacted]

OCT 20 19

BACK

Contents: 1 System

Dosage & Administration: Follow dosing instructions as directed by your physician. For application, see patient instructions.

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH

Storage: Do not store above 30°C (86°F).

See patient instructions for disposal information.

Contains NICOTINE, the addictive agent in cigarettes.

Inactive Components: Silicone adhesive, acrylate adhesive, and aluminized polyester.

Manufactured by:
SANO CORPORATION
Miramar, FL 33025

ZL012 09/95

OCT 20 1997

FRONT

Nicotine Transdermal System

21 mg/day

FOR TRANSDERMAL USE ONLY

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ZL001 09/95

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OCT 20 1997

[redacted]

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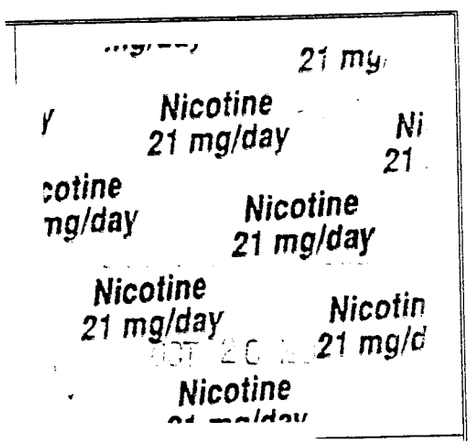
Manufactured by:
SANO CORPORATION
Miramar, FL 33025

ZL012 09/95

OCT 20 1997

'day


21 mg
Nicotine
21 mg/day
Ni
21
cotine
ng/day
Nicotine
21 mg/day
Nicotine
21 mg/day
Nicotin
21 mg/d
Nicotine

Dosage & Administration:
Follow dosing instructions as directed by your physician. For application, see patient instructions.

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.

Storage:
Do not store above 30°C (86°F).

See patient instructions for disposal information.

Contains NICOTINE, the addictive agent in cigarettes.

See bottom panel for lot number and expiration date.

Nicotine Transdermal System

Contents: 30 Transdermal Systems

FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.

21 mg/day

One 29 cm² system which contains 47.3 mg of nicotine.

Caution: Federal law prohibits dispensing without prescription.

21
mg/day

Contents: 30 Transdermal Systems
For Transdermal Use Only

Nicotine Transdermal System

Contents: 30 Transdermal Systems

FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.

21
mg/day

One 29 cm² system which contains 47.3 mg of nicotine.

Caution: Federal law prohibits dispensing without prescription.

Inactive Components:
Silicone adhesive, acrylate adhesive, and aluminized polyester.

Manufactured by:
Sano Corporation
Miramar, FL 33025

3 3215-1236-30 5

Contents: 14 Transdermal Systems
For Transdermal Use Only

Inactive Components:
Silicone adhesive, acrylate adhesive, and aluminized polyester.

Manufactured by:
Sano Corporation
Miramar, FL 33025

3 3215-1236-14 5

Nicotine Transdermal System

Contents: 14 Transdermal Systems

FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.

21 mg/day

One 29 cm² system which contains 47.3 mg of nicotine.

Caution: Federal law prohibits dispensing without prescription.

Dosage & Administration:
Follow dosing instructions as directed by your physician. For application, see patient instructions.

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.

Storage:
Do not store above 30°C (86°F).

See patient instructions for disposal information.

Contains NICOTINE, the addictive agent in cigarettes.

See bottom panel for lot number and expiration date.

Nicotine Transdermal System

Contents: 14 Transdermal Systems

FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.

21 mg/day

One 29 cm² system which contains 47.3 mg of nicotine.

Caution: Federal law prohibits dispensing without prescription.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074612

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-612

3. NAME AND ADDRESS OF APPLICANT

Sano Corporation
Attention: Diane Servello
3250 Commerce Parkway
Miramar, FL 33025

4. LEGAL BASIS for ANDA SUBMISSION

page 100007
Listed Drug: Habitrol™ Nicotine Transdermal System/Ciba Corporation
Patent#s 5016652 and 4597961 expire 5.21.2008 and 7.1.2003, respectively. Exclusivity expired 11.7.94.

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Nicotine Transdermal System

8. SUPPLEMENT(s) PROVIDE(s) FOR: None

9. AMENDMENTS AND OTHER DATES:

Applicant:

01.20.95: Original
04.13.95: Amendment (Debarment Certification)
04.24.95: Amendment (Notice of certification of noninfringement of patent#s 5016652 and 4597961
06.07.95: Correspondance
10.20.95: Amendment
11.01.95: Amendment
02.12.96: Amendment
02.12.96: Amendment
06.04.96: Amendment
07.31.96: Amendment
08.14.96: Amendment
10.10.96: Amendment
02.12.97: Amendment **Subject of this review**
05.09.97: Amendment **Subject of this review**

08.28.97 - Fax amendment **Subject of this review**
09.02.97 - Fax amendment **Subject of this review**

FDA:

4.6.95: Acknowledge receipt
08.16.95: NA letter #1
05.29.96: NA letter #2
01.14.97: NA letter #3
04.25.97: NA letter #4
08.28.97: Phone request

10. PHARMACOLOGICAL CATEGORY

Relief of Nicotine Withdrawal

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s) See review element #37

13. DOSAGE FORM

Transdermal Patch

14. POTENCY

21 mg/day

15. CHEMICAL NAME AND STRUCTURE

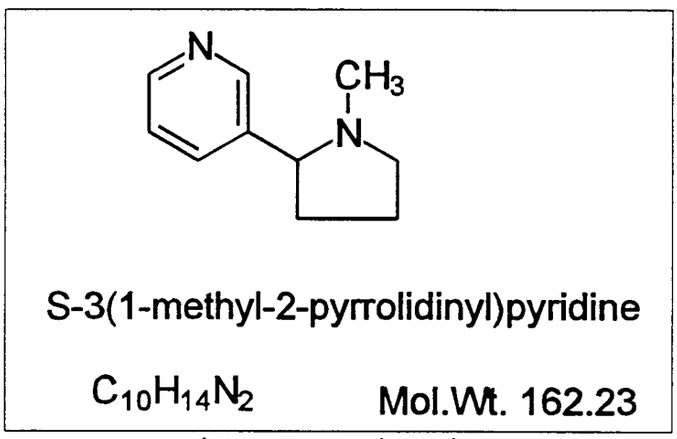


Figure 1: Nicotine

16. RECORDS AND REPORTS None

17. COMMENTS

a. The following DMFs are satisfactory:
b. The Chemistry, Manufacturing, and Controls are satisfactory.
c. Compendial drug substance and drug product. MV satisfactory, Southeast Regional Labs, 9.19.96.
d. EER submitted 4.3.96; satisfactory, 7.22.96; updates requested.
e. Professional labeling - J. White, satisfactory, 3.18.97.
f. Bio-review satisfactory, per F. Nouravarsani, 08.27.97.
g. The skin irritation studies have been found satisfactory, M. M. Fanning, 7.25.97.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is satisfactory in chemistry, manufacturing and controls, labeling and bio-review. It may be approved.

19. REVIEWER: DATE COMPLETED:

U. V. Venkataram, Ph.D. 07.12.97, 09.02.97 (revised)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074612

BIOEQUIVALENCE REVIEW(S)

MAR 2 4 1997

Nicotine Transdermal System
21 mg/day
ANDA #74-612
Reviewer: F. Nouravarsani
74612W.796

Sano Corporation
Miramar, FL
Submission Date:
July 31, 1996

REVIEW OF A WAIVER REQUEST

The firm met with the agency on July 01, 1996 to amend the status of the Major-Not Approvable Letter of May 24th. The firm has stated that: "This decision was based on the Office's request for data on new confirmatory batches manufactured using the proposed 12% overage to demonstrate that the actual loss creates the need for a 12% and not the 7% contemplated in the original (Miramar) submission."

The firm has provided the information requested at the July 1st meeting as the chemistry and bioequivalence amendments to its May 31, 1996 responses, and requested a waiver of bioequivalence study requirements for the confirmatory batches manufactured with a proposed overage of 12%.

The firm's bioequivalence study conducted on its test product, Nicotine Transdermal System, 21 mg/day (lot #95E01111) has been found incomplete. Therefore the firm should be informed that, this submission will not be reviewed at this time.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE for RMH 3/12/97

Concur: _____ Date: 3/24/97
Nicholas Fleischer, ... D.
Director
Division of Bioequivalence

FNouravarsani/03-07-97/74612W.796

CC: ANDA #74-612 (original, duplicate), Nouravarsani, HFD-658, Drug File, Division File

Nicotine Transdermal System
ANDA #74-612, 21 mg/day
ANDA #74-611, 14 mg/day
ANDA #74-645, 7 mg/day
Reviewer: F. Nouravarsani
74612ASD.497

Sano Corporation
Miramar, FL
Submission Date:
April 25, 1997
May 09, 1997
June 04, 18, 19, 1997
July 02, 03, and 15, 1997

REVIEW OF A SINGLE- AND MULTIPLE-DOSE BIOEQUIVALENCE STUDIES AMENDMENTS, IRRITATION STUDY AMENDMENT, DISSOLUTION TESTING, AND TWO WAIVERS REQUEST

Sano Corporation had previously submitted a combined single- and multiple-dose bioequivalence studies, and dissolution testing conducted on its test product, Nicotine Transdermal System, 21 mg/day and the listed reference product, Habitrol, 21 mg/day (N20076-003, Nov. 27, 1991) by Ciba (Basel Pharmaceuticals). The firm had also submitted an irritation study for its Nicotine Transdermal System, 7 mg/day.

In the current submissions (April 25 and May 09, 1997) the firm responded to the deficiencies letter and has requested waivers of bioequivalence studies requirements for its test products, 7 mg/day and 14 mg/day Nicotine Transdermal Systems. At request of the reviewer, the firm submitted computer diskettes containing the bioequivalence studies data on June 04, 18, and 19, 1997; and also submitted requested information regarding lots used in the drug release test and content uniformity for its test products on July 02 and 03, 1997. In the latest submission, July 15, 1997, the firm submitted an additional skin irritaion study comparing the test and reference products (in the first irritation study, the test was not compared with the reference product).

Deficiencies #1 and #2:

The firm had submitted 90% CI, and had stated that "Standard Error of Estimate" was used to calculate the 90% CI. However, the firm had not submitted a complete report of the data analyses including the values of the "Standard Error of Estimate". The firm was requested to submit these information. The firm was also requested to submit details for calculation of 90% CI.

Response to deficiencies #1 and #2:

The firm submitted additional information. However, the firm should be informed that there is error in calculation of 90% CI. Furthermore degrees of freedom (df) for sequence was reported 3

instead of 1 in statement reports of ANOVA for the parameters of multiple-dose study at steady state.

The reviewer analyzed the data using SAS-GLM procedure, and the 90% CIs were recalculated for AUCs and Cmax for both single and multiple dose studies.

	90% CI, Ln-Transformed	
Parameters	Single-Dose	Multiple-Dose
AUC(0-24) hr*ng/mL	95.07-117.37	92.4-105.0
AUC(0-t) hr*ng/mL	91.94-111.74	--
AUC(0-Inf)* hr*ng/mL	92.78-111.36	--
C(Max) ng/mL	98.90-119.05	95.4-110.6

*: KE used in calculation of the AUC(0-Inf) was obtained using T13-T17.

The 90% CIs fall in the required range by the Division of Bioequivalence.

Deficiency #3:

Comparisons of the mean plasma concentrations of nicotine at 4 days (96 hr), 5 days (120 hr), and 6 days (144 hr) show a slight increase for both the test and reference products by increasing the time. The assessment of steady state should be explained.

Response to deficiency #3:

The firm stated that a "repeated measures analysis of variance (ANOVA) model was used to evaluate for time differences". Factors included in the model were: sequence, subject within sequence, period, period by sequence interaction, period by subject within sequence interaction, hour, hour by sequence interaction, hour by subject within sequence interaction, hour by period interaction, hour by period by sequence interaction, and hour by period by subject within sequence interaction. The specific interests were the hour and hour by period by sequence

interaction terms. The firm concluded steady state for the studies since neither the hour term, nor the hour by period by sequence interaction term was significant ($p>0.05$).
The steady state was confirmed using a proposed program by Dr. Andre Jackson (Division of Bioequivalence).

Deficiency #4:

The firm was informed that the value of C(Min) used in the calculation of the Degree of Fluctuation was apparently determined as the lowest concentration of the nicotine or cotinine. The C(Min) value is the "drug concentrations at the end of each dosing interval during steady state" (Division of Bioequivalence Guidance: Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design dated July 1st, 1992).

The firm was requested to use correct value of C(Min) in calculation of percentage Degree of Fluctuation (DF%).

Response to deficiency #4:

The firm used "drug concentration at the end of dosing interval during steady state" (concentration at 168 hour) in calculation of the degree of fluctuation.

The response is acceptable.

Deficiency #5:

Subject #9 discontinued the study for adverse events. The samples were collected for the single dose, reference product, first period. The data were used in the analysis of single-dose.

A total of 47 samples were reported for this subject, although 37 samples should have been reported (21 blood samples (0-72 hrs), 6 QC, 8 standards, 1 SYS, and 1 blank). The firm was requested to clarify.

Response to deficiency #5:

The firm responded that samples from subjects #9 and #19 were assayed on the same standard curve.

The response is acceptable.

Deficiency #6:

Report of the "peak area" for subject #18 shows 59 samples for nicotine instead of 94. The firm was requested to clarify.

Response to deficiency #6:

The firm responded that page including samples #60-94 for this subject was likely missed during copying, and therefore was not submitted to the agency on August 06, 1996. The firm submitted a copy of this page with its current amendment submission.

The response is acceptable.

Deficiency #7:

Subject #19 completed only first 12 hours of the study (total samples should be 25), but 74 samples were reported for the nicotine and cotinine including standards, QCs, blank, and SYS. The firm was requested to clarify.

Response to deficiency #7:

The firm responded that "the standard curve NIC_019 refers to subject #20, not 19". The samples from subject #19 were assayed on curve NIC_009.

The response is acceptable.

Deficiency #8:

Subject #20 did not complete the multiple-dose study for the period 2 (test product), but 95 samples were reported. The firm was requested to clarify.

Response to deficiency #8:

The 74 samples for subject #20 were assayed on NIC_019.

The response is acceptable.

Deficiency #9:

The "peak area" for some report show a total of 95 runs instead of 94. The firm was requested to clarify.

Response to deficiency #9:

The firm responded that "samples for a particular subject were not necessarily done using the same standard curve." For example, sample at 38 hour, period 2 for subject #18 was run on NIC_027, and NIC_028. Therefore, there was 94 samples instead of 95 for NIC_018.

The response is acceptable.

Deficiency #10 (Drug Release Test):

The proposed ranges of specifications for the dissolution testing did not cover the dissolution of the reference product. However, the firm was requested to submit dissolution testing data, comparing the test and reference products using an appropriate Drug Release Test reported in the USP 23, Supplement #5.

Response to deficiency #10:

The firm has submitted in vitro drug release rate study for both test and reference products using USP drug release method (USP 23, Supplement 5). The following products were used in the study:

In Vivo Delivery	Lot# Test	Lot# Ref.	Size, Cm^2 Test	Size, Cm^2 Ref.	Nicotine/Unit, mg Test	Nicotine/Unit, mg Ref.
7 mg/day	96B06112	13011476	9.7	10	15.8	17.5
14 mg/day	96B03111	13011466	19.3	20	31.5	35.0
21 mg/day	96B10111	23011396	29.0	30	47.3	52.5

The conditions were as follows:

Apparatus:	Apparatus 6, shaft, cylinder and vessel assembly (USP 23)
Sample holder:	Double-sided tape on the cylinder
Medium:	Phosphate Buffer (137 mM NaCl, 2.7 mM KCl, 6.4 mM $Na_2HPO_4.7\ H_2O$, 1.5 mM KH_2PO_4
Volume:	500 mL
Bath Temp.	32.0 $\pm$ 0.5° C
Paddle Speed:	50 rpm
Sampling:	10 mL aliquots at 6 and 24 hours

Tolerances: USP 23: "The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified conforms to Acceptance Table 4."

The criteria for the Acceptance Table 4 is: "The average value of the 12 units (L1+L2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range."

Amount dissolved at 6 hours: between
Amount dissolved at 24 hours: between

Results of The Drug Release Test:

The reported mean values (12 units) for each test and reference products at 6 and 24 hours are within the specified tolerances for each product strength. There is no individual value outside the stated range (Table 1).

The lots used in the drug release test for the test and reference products, 21 mg/day are not the same lots used in the bio-studies. The firm has explained (July 02, 1997) that the reference product lot (#1301016J) was expired on January 1996, and the proposed expiration date for the the test product is 24 months. Since the test product, lot #95E01111 was manufactured in May 1995, it was expired in April 1997.

Content Uniformity:

Content uniformity was reported for each lot used in the drug release test. The mean (CV%, N) content uniformity of 99.4% (1.3%, N=10), 99.5% (3.7%, N=10), and 102% (2.4%, N=10) were obtained for the products of 7 mg/day (lot #96B06112), 14 mg/day (lot #96B03111), and 21 mg/day (lot #96B10111), respectively. The mean (CV%) content uniformity of the 21 md/day product, lot 95E01111 used in bio-study was reported to be 95.9% (5.2%).

The response is acceptable.

Deficiency #11:

Clinical Reviewer's Evaluation for Nicotine Transdermal System, 7 mg/day:

Validity of the methodology used in the study (submission date: October 20, 1995) could not be evaluated by the clinical reviewer, because the method was apparently derived empirically

based on experience with cosmetics of low irritation potential. Furthermore, the use of a mean total group score for 10 subjects might obscure the occurrence of high scores for some of the subjects.

The clinical reviewer recommended that the sponsor perform an additional irritancy study which compares the firm's product to the marketed Nicotine Transdermal Patch.

Response to deficiency #11:

The firm requested that agency to reconsider the data submitted by the firm in support of the skin irritation study (submission dated April 25, 1997).

The firm's request was reviewed by Mary M. Fanning, M.D., Ph.D., Associate Director of Medical Affairs, OGD. An irritation study to compare the test product to the reference product was required. A copy of "SUMMARY OF DECISION RE: REQUIREMENT OF SKIN IRRITATION STUDIES" dated June 20, 1997 is attached.

In response to the above requirement, the firm submitted an additional skin irritation study to compare the test and reference products (submission date: July 15, 1997). The study was reviewed by Dr. Mary M. Fanning (Attached Review dated July 18, 1997). The conclusion and recommendation of the review state that:

"The Sano Nicotine Transdermal System has skin irritation potential which is close to but slightly less than that seen with the reference listed drug, Habitrol Nicotine Transdermal System. The Sano Nicotine Transdermal System should be defined as bioequivalent to Habitrol Nicotine Transdermal System with respect to skin irritation."

Attached is also E-MAIL from Dr. Phyllis Huene indicating her agreement with Dr. Fanning review.

Waivers Request for 7 mg/day and 14 mg/day Products:

The firm has requested waivers of bioequivalence study requirements for its 7 mg/day and 14 mg/day products based on the followings:

1. The 7 mg/day and 14 mg/day Nicotine Transdermal Systems are the same dosage form as the 21 mg/day, and their active and inactive ingredients are also proportionally similar to the 21 mg/day product, which has been shown to be bioequivalent to

the reference product (Table 2).

2. All three products of Nicotine Transdermal Systems have been tested by an in-vitro test (Table 1).

COMMENTS:

1. The firm should be informed that there is an error in calculation of the 90% CI. Furthermore degrees of freedom (df) for sequence effect was reported 3 instead of 1 in statement reports of ANOVA for the parameters of multiple-dose at steady state.

However, the reviewer analyzed the data using SAS-GLM procedure, and the 90% CIs were recalculated for AUCs and Cmax for both single and multiple dose studies. The 90% CIs fall in the required range by the Division of Bioequivalence.

2. The single-dose and multiple-dose bioequivalence studies were found acceptable by the Division of Bioequivalence. However, the bioequivalence studies should be inspected by the Division of Scientific Investigations, since the test product is the first generic Nicotine Trasdermal System with acceptable bioequivalence studies.

3. The waivers of bioequivalence studies requirements may be granted for the 7 mg/day and 14 mg/day products.

DEFICIENCY: None.

RECOMMENDATIONS:

1. The single-dose, fasting bioequivalence study submitted by SANO Corporation on its Nicotine Transdermal System, 21 mg/day (lot #95E01111) comparing it to Habitrol, 21 mg/day (lot #1301016J) by Ciba (Basel Pharmaceuticals) has been found acceptable by the Division of Bioequivalence.

2. The multiple-dose, fasting bioequivalence study submitted by SANO Corporation on its Nicotine Transdermal System, 21 mg/day (lot #95E01111) comparing it to Habitrol, 21 mg/day (lot #1301016J) has been found acceptable by the Division of Bioequivalence.

3. The irritation study submitted by SANO Corporation on its Nicotine Transdermal System, 7 mg/day (lot #96B06112) comparing it to Habitrol, 7 mg/day (lot #13011496) by Ciba (Basel Pharmaceuticals) has been found acceptable.

4. The dissolution testing conducted by SANO Corporation on its Nicotine Transdermal System, 21 mg/Day (lot #96B10111) has been found acceptable by the Division of Bioequivalence.

5. The dissolution testing conducted by SANO Corporation on its Nicotine Transdermal Systems, 7 mg/day (lot #96B06112) and 14 mg/day (96B03111) is acceptable. The firm has conducted acceptable in-vivo bioequivalence studies (submission dated October 20, 1995) comparing its 21 mg/day, Transdermal System of the test product with 21 mg/day, Transdermal System of the reference product, Habitrol manufactured by Ciba (Basel Pharmaceuticals). The formulations for the 7 mg/day and 14 mg/day strengths are proportionally similar to the 21 mg strength of the test product which underwent bioequivalency testing. The waivers of in-vivo bioequivalence study requirements for the 7 mg/day and 14 mg/day Transdermal Systems of the test product is granted. The 7mg/day and 14 mg/day Transdermal Systems of the test products are therefore deemed bioequivalent to the 7 mg/day and 14 mg/day Transdermal Systems of Habitrol manufactured by Ciba (Basel Pharmaceuticals).

6. The drug release testing should be incorporated into the firm's manufacturing controls and stability program. The test should be conducted in 500 mL of phosphate buffer at 32° C using USP 23 apparatus 6, 50 rpm. The test product should meet the following specifications:

Amount dissolved at 6 hours: between
Amount dissolved at 24 hours: between

7. The single- and multiple-dose bioequivalence studies submitted by SANO Corporation on its Nicotine Transdermal System, 21 mg/day (lot #95E01111) comparing it to Habitrol, 21 mg/day (lot #1301016J) by Ciba (Basel Pharmaceuticals) should be inspected by the Division of Scientific Investigations, since the test product is the first generic Nicotine Transdermal System with acceptable bioequivalence studies.

The firm should be informed of the COMMENT #1.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRL 8/27/97

Concur: _____ Date: 9/18/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/08-20-97/74612ASD.497

CC: ANDA #74-612 (original, duplicate), HFD-650 (Director), HFD-658 (Nouravarsani), Drug File, Division File

Table 1: In Vitro Drug Release Testing

Drug (Generic Name): Nicotine Transdermal System
Dose Strength: 21 mg/Day, 14 mg/Day, 7 mg/Day
ANDA: #74-612, 74-611, 74-645
Firm: Sano Corporation
Submission Date: May 09, 1997

I. Conditions for Dissolution Testing:

USP XXIII, Apparatus 6 RPM 50 No. Units Tested 12

Medium: Phosphate Buffer ($NaCl$, KCl, $Na_2HPO_4 \cdot 7H_2O$, KH_2PO_4) Volume: 500 mL at 32° C

Reference Drug: Habitrol

Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

Sampling Times, Hours	Test Product: Lot #96B10111 In Vivo Delivery 21 mg/day Size 29 Cm^2 Nicotine/Unit 47.3 mg			Reference Product: Lot #23011396 In Vivo Delivery 21 mg/day Size 30 Cm^2 Nicotine/Unit 52.5 mg		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
6	129		(4.2)	110		(0.5)
24	187		(3.5)	195		(1.4)

Sampling Times, Hours	Test Product: Lot #96B03111 In Vivo Delivery 14 mg/day Size 19.3 Cm^2 Nicotine/Unit 31.5 mg			Reference Product: Lot #13011466 In Vivo Delivery 14 mg/day Size 20 Cm^2 Nicotine/Unit 35.0 mg		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
6	131		(2.5)	113		(0.9)
24	189		(2.2)	198		(1.5)

Sampling Times, Hours	Test Product: Lot #96B06112 In Vivo Delivery 7 mg/day Size 9.7 Cm^2 Nicotine/Unit 15.8 mg			Reference Product: Lot #1301147[illegible] In Vivo Delivery 7 mg/day Size 10 Cm^2 Nicotine/Unit 17.5 mg		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
6	127		(5.8)	116		(1.1)
24	184		(5.2)	199		(1.1)

Table 2:

Formulation Comparison:

Ingredients	%W/W,Dry	mg/Cm^2	7mg/day 9.7 Cm^2	14mg/day 19.3 Cm^2	21mg/day 29.0 Cm^2
Nicotine		--	15.81mg	31.46mg	47.27mg
Acrylic Adhesive					
Silicone Adhesive					
Release Liner					
Backing					
Total	100	48.49	470.35mg	935.86mg	1406.21mg

Attachments:

SANO NICOTINE TRANSDERMAL PATCHES

SUMMARY OF DECISION RE: REQUIREMENT OF SKIN IRRITATION STUDIES

June 20,1997

A meeting was held with Sano Corporation on June 12, 1997 to discuss the requirement for a skin irritation study comparing test versus reference for their product. The company wanted their completed study, which compared test versus controls, to be considered sufficient to meet this requirement.

In follow-up to that meeting, materials were circulated among OGD staff as well as Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products. These are described in the attached e-mail of June 17, 1997. A meeting was scheduled for June 20, 1997, but other pressing matters made it impossible for Dr. Wilkin to attend. The issues were summarized for him in an e-mail of June 18, 1997, in preparation for a telephone discussion the following day. Although this did not occur, the summary and background material permitted Dr. Wilkin to come to a decision.

Dr. Wilkin found it difficult to evaluate what no to minimal irritation would be in the classification system used in the study. He did note, however, that while the low irritancy control was in the range of 5.7 to 14.3, the Nicotine patch scored considerably higher at 80.5. The patch alone had a score of 173.4 and the explanation given for it's higher irritancy was the presence of components in the patch material which were irritating. Dr. Wilkin took a pragmatic, clinical approach and identified the clinical significance of the various scores. He denoted a 1+ reaction as noticeable and a 2+ as irritating/bothersome. A 3+ reaction is one that leads to discontinuation of application of the patch at the site because the skin reaction is sufficiently serious. In addition, the company scored the sites for other elements of an inflammatory reaction.

When the primary data was reviewed using these criteria, the potential irritancy of the Nicotine patches was more than "no or minimal irritation". The Nicotine patch group consisted of 29 subjects. Of these, 21 had a maximum score of 1+, 4 had a maximum score of 2+ and 1 reached a score of 3+. Three subjects had no reaction. In addition, 3 of the subjects who scored 1+ had glazing and 1 had glazing with peeling and cracking. Two of those who scored 2+ experienced either glazing with peeling and cracking or small petechial erosions and/or scabs. The subject with the most severe reaction (3+) experienced glazing with fissures and small petechial erosions and/or scabs. By day 7, 45% had 1+ or greater scores and by day 8, this had risen to 55%.

Based upon these observations it was determined that the irritation potential for

this product was significant and that another study comparing the Sano Nicotine patch study to the RDL was required. This information was communicated to Sano's consultant. Robert Pollock by Mary Fanning and Gordon Johnston on June 20, 1997. In addition, Diane Servello of Reguiatory Affairs at Sano Corporation subsequently spoke with Doug Sporn about the required study and their time line.

Mary M. Fanning
Associate Director of Medical Affairs
Office of Generic Drugs

Medical Officer Review
July 18, 1997

ANDA 74-612 ; Nicotine Transdermal System, 21 mg/day
ANDA 74-611 ; Nicotine Transdermal System, 14 mg/day
ANDA 74-645 ; Nicotine Transdermal System, 7 mg/day

Product: Nicotine Transdermal System, 21 mg/day, 14 mg/day, 7 mg/day

Reference Listed Drug: Habitrol Nicotine Transdermal System (Ciba)

Applicant: Sano Corporation

Submission Date: January 20, 1995
Resubmission Date: October 20, 1995
Resubmission Date: July 15, 1997

SKIN IRRITATION STUDY

Regulatory History:

This application was originally submitted in January 1995. Due to a move of the company's manufacturing plant from Plantation to Miramar, Florida, the application was re-submitted in October, 1995, following the completion of additional studies required by this move. The skin irritation study submitted with the original application was reviewed by the Division of Dermatologic and Dental Drug Products following the resubmission. This study was not approved. The Division concluded that the study did not support the bioequivalence of the Sano Nicotine Transdermal System and the Reference Listed Drug (Habitrol - Nicotine Transdermal System) as it pertained to skin irritancy.

In this study, the firm had compared their product to patch alone and to two standard low and high irritancy controls, but not to the Reference Listed Drug (RLD). In addition, several other problems were noted such as a small sample size, use of a non-validated scoring system and the averaging of results which could obscure high and low responders. At the firm's request, this decision was revisited,

both in a formal reevaluation of the data from this study demonstrating the degree of irritancy of the Sano product, as well as during a presentation made by the company to FDA/OGD on June 12, 1997. After full evaluation of all the information available and consideration of all the issues, the Office of Generic Drugs, in collaboration with the Division of Dermatologic and Dental Drug Products, upheld the original decision. The company was informed of the decision and they were advised to repeat the skin irritation study comparing their product to the Reference Listed Drug. The following skin irritation study was submitted for evaluation on July 15, 1997.

Clinical Study Protocol Number: P123-1197

Protocol Title: Evaluation of Cumulative Irritation Potential in Humans 21-Day Test for Nicotine Transdermal Patch

Study Objective:

The objective of this study was to test the comparative human skin irritation potential elicited by the repetitive topical application (over 21 days) of test articles which included the test drug, reference listed drug and two standard high and low irritancy controls.

Study Design:

This was a blinded (both to subject and scorer of skin irritancy) study comparing the skin irritation of four test articles. The four test articles were:

1. Nicotine Transdermal System, 7 mg/24 h
2. Habitrol - Nicotine Transdermal System, 7 mg/24 h
3. Sodium Lauryl Sulfate [SLS] 0.1% (high irritancy control)
4. Physiologic Saline 0.9% (low irritancy control)

The two control articles were applied to the skin by pipette for a total volume of 0.2 ml. This was occluded by application of a non woven cotton pad covered and held in place along the full perimeter by occlusive hypoallergenic tape.

Target enrollment was set so as to have thirty completed subjects, i.e., those who fulfilled the enrollment screening and completed all visits. Inclusion and exclusion criteria were as follows:

Inclusion Criteria (All criteria had to be satisfied)

1. Subjects must be ambulatory, 18-60 years of age and in reasonably good health.
2. Female subjects must be surgically sterile, postmenopausal, or using an acceptable method of birth control.
3. Minor deviations in normal medical history, physical examination and clinical laboratory results (including electrocardiogram), considered to be clinically insignificant by the Investigator/Sub-Investigator and the Sano Corporation Monitor will be permitted.
4. Subjects must have normal vital signs (for their age group) and be free of any recognizable medical problem.
5. Subjects must undergo and pass a routine physical examination within two weeks prior to entrance into the study.
6. Subjects must smoke at least one pack of cigarettes per day confirmed by urinary Cotinine levels.
7. Subjects must read and sign the informed consent statement.

Exclusion Criteria (none of these may be present)

1. A history of diabetes.
2. A history or presence of significant hepatic, renal, endocrine, cardiac, hypertensive (blood pressure greater than 160/90 mm Hg), nervous, gastrointestinal, pulmonary or metabolic disorders.
3. Hypotension (blood pressure less than 100/60 mm Hg).
4. A history of hyperthyroidism, or pheochromocytoma.
5. A history of cerebral, coronary or peripheral vascular disease.
6. A history or presence of glaucoma or organic pyloric stenosis.
7. A course of drug therapy within four weeks prior to the study, which may affect the safety of the volunteers.
8. Any condition or history that the Investigator considers might increase the risk to the individual or interfere with the evaluation of data.
9. All laboratory test results must be within normal limits for this age group (especially SGOT and SGPT), except those test results that are determined by the Investigator to have no clinical significance to the study.
10. Tattoos, scar tissue or any other skin condition at the site of drug application which might alter absorption through the skin. Such conditions as sunburn, skin peeling from an earlier sunburn, acne or bruises on the skin will exclude any subject from participating.
11. Women who are pregnant or nursing or who are not taking medically accepted contraceptive measures.
12. A history of atopic or eczematous dermatitis.
13. Allergy to nicotine.
14. Previous exposure to nicotine patches.

15. Mastectomy for cancer involving removal of lymph nodes.
16. Participation in any patch test for irritation or sensitization within the past four weeks.
17. Routine high dosage use of anti-inflammatory drugs (aspirin, ibuprofen, corticosteroids), immunosuppressive drugs or antihistamine medication (steroid nose drops and/or eye drops are permitted).
18. Severe asthma.
19. Immunological disorders such as HIV, AIDS and systemic lupus erythematosus.
20. Use of topical drugs at patching site.
21. A history of non-compliance or a subject who is considered potentially unreliable.
22. Allergy to adhesives, tapes, etc.

The four test articles were applied in a randomized way to a series of skin sites in the paraspinal regions. All subsequent applications of the same test article were made at the original (day 1) site. The assignment of skin sites was varied in a random way so that each test article occupied each skin site within the group of study subjects with approximately equal frequency, in an effort to eliminate position or order bias. The test articles were applied to their designated sites once daily over the twenty-one days of the study period for contact periods lasting 23+/-1 hours. Following patch removal, a 24 hour score was obtained and a new patch was subsequently re-applied. If patches fell off during the 23 hour period they were not re-applied. This event was reported to the Investigator and recorded in the case report form.

Subjects were evaluated for signs of irritation at the application area prior to study entry on Day 1. Measurement of skin irritation was done by an experienced technician and the protocol stated that efforts were made to have a single person do all the evaluations. The skin site was observed using a 100 watt incandescent blue lamp as the artificial light source. The person doing the scoring was blinded to treatment assignments and to previous scores. Reactions were scored daily, 24 hours after application, using the following two-part scale:

<u>Effect on skin:</u>

0 No evidence of irritation
1 Minimal erythema, barely perceptible
2 Definite erythema, readily visible; or minimal edema; or minimal papular response
3 Erythema and papules
4 Definite edema
5 Erythema, edema and papules
6 Vesicular eruption

7 Strong reaction spreading beyond test site

Effect on superficial layers of the skin:

A Slight glazed appearance
B Marked glazing
C Glazing with peeling and cracking
F Glazing with fissures
G Film of dried serous exudate covering all or a portion of the patch site
H Small petechial erosions and/or scabs

Several maximum limits were defined for these scores. When a numerical score of 3, 4, 5, 6, or 7 was reached or any numerical score was appended with the letter grade of F, G, or H, no further applications of test material were made. However, this site continued to be scored to the end of the 21 day study period. In this situation, a score of 3 was entered for all scores through the remainder of the study. The letter grades were converted to numerical scores as follows: A = 0, B = 1, C = 2 and F, G and H = 3. These numerical equivalents were considered additive to the numerical score (e.g., 2C = 2 + 2 = 4). They were added in the calculation of the total irritancy score for the entire cohort. The upper limit individual score selected was 3. All scores were calculated and those above this were entered as 3 in order to maintain the focus on evaluation of mild irritation expected for these products. Statistical analysis was carried out on the total irritation, Base 10 scores and the Friedman Rank Sums method.

Adverse events were documented and recorded on the case report forms. Severity and relatedness to test material was determined by the Investigator.

Study Conduct:

The study was conducted between May 28 and June 30, 1997. Fifty-nine subjects were screened and 16 of those screened were excluded. Of these sixteen, 5 were excluded due to medical or laboratory abnormalities, 5 had conflicts with the expected time commitment of the study, 2 had negative Cotinine urinary levels, 2 had previous recent exposure to nicotine patches and 2 experienced difficulty with study conduct. Therefore, 43 subjects were entered (29 females and 14 males) into the study. Twelve did not complete the study for the following reasons: work schedule (3), decided not to participate further in the study (2), medical illness (1), car trouble (2), severe sunburn (2), no show (1) and adverse event (1). This left a cohort of 31 subjects (21 females and 10 males) who completed the study.

Seventy-two protocol deviations occurred during the study. All of these deviations

involved either the interval between receiving a patch and having an evaluation completed or the duration of time the patch was worn. Three individuals had skin evaluations done more than 24 hours after patch application (26-30 h), on one study day each . Patches were worn for periods less than 23 +/- 1 hours by 23 subjects. This most often involved only one of the four patches applied. It was seen most frequently with Habitrol Nicotine Transdermal System (48 patches), followed by Nicotine Transdermal System (28 patches). Physiologic saline (6) and sodium lauryl sulfate patches (2) lost adherence much less frequently. These protocol deviations occurred primarily on Day 1 and 2 of the study involving 13 and 7 patches, respectively. There were 4 subjects who had >3 repeated episodes (range 4-8). The remaining subjects experienced more isolated events with 7 deviating on only one day, 5 on two days and 6 on three separate occasions.

Study Results:

All primary data was provided by the Applicant and reviewed by the Medical Officer in tandem with review of the mean and cumulative data presented by the Applicant.

Freidman rank sum analysis

The mean score was calculated for all the subjects on each day of the study per test group. Multiple comparison test results derived from the Freidman rank sum analysis showed the following statistically significant results (> = significantly more irritating):

A > C	on	day 1	B > A	on	day 5, 10, 12, 13, 14, 15, and 21
A > D	on	day 1 - 21	B > C	on	day 1
			B > D	on	day 1 - 21

C > A	on	day 3 - 21, and overall
C > B	on	day 3 - 16, 19 - 21, and overall
C > D	on	day 1 - 21

A=Sano Nicotine Transdermal System
B=Habitrol Nicotine Transdermal System
C=Sodium Lauryl Sulfate
D=Normal Saline

Days Until Patch Removal

Patches were removed when the irritancy reached a score of 3 or more on the scale listed previously. The mean number of "days until removal" of a patch were calculated for each test product. The saline control had an average of 22.00 days until patch removal was required. The high irritancy control, sodium lauryl sulfate patches, required removal at a mean of 3.79 days. The test products were less irritating than this. Nicotine Transdermal System lasted for a mean of 19.1 days until the patch had to be removed for significant skin reactions. Habitrol Nicotine Transdermal System patches were removed at a mean of 15.56 days. These data were subjected to an analysis of variance which yielded a p-value of 0.0001. Both test products were significantly different from the high and the low irritancy controls. In addition, the Sano product was applied to the skin for significantly more days than the Habitrol Nicotine Transdermal System.

Total and Mean Irritancy Scores

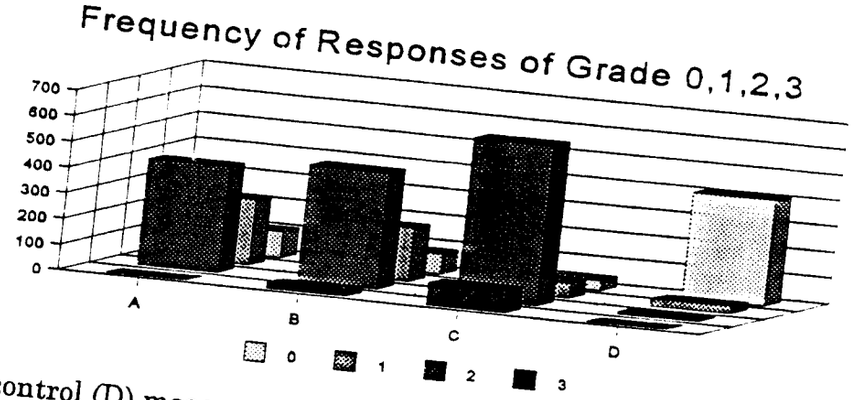
The mean of the individual subject total irritancy scores over the course of the study as well as the total irritancy scores for all subjects for each test arm were calculated. These are derived by adding the score per subject per day and either adding the score for each of the subjects (Total irritancy score) or averaging the score of the group of subjects to derive the mean score. The respective scores are presented in the following table (per Applicant):

Test Article	Grand Total	Mean	Standard Deviation
A	1410	67.1	16.2
B	1585	75.5	24.3
C	2178	103.7	23.7
D	48	2.3	4.3

Both the mean and grand total sum shown in this Table demonstrate a wide interval between the high and low irritancy controls' results. The two test articles have scores that are similar to each other but intermediate between the high and low irritancy controls. In all measurements, the scores for the Sano product were less than those seen with the Habitrol product.

Frequency of Grade Responses

The cumulative frequency of each score (0-3+) was derived for the 4 study groups over the full course of the study to a maximum of 903 potential measurements (21 days x 43 subjects). This is depicted in the following graph (per Medical Officer - raw data provided by Applicant in Table format):



The saline control (D) measurements were primarily 0 with a small number of 1+ scores. The high irritancy control (C) led to frequent responses of 2+ with a significant number of 3+ measurements as well. The two test products were similar. However, the Sano product elicited no 3+ and fewer 2+ responses, more 1+ and more 0 responses than did Habitrol. In addition, Habitrol elicited a number of 3+ responses. Both of these products were less irritating than the high irritancy control.

Qualitative Observations

A qualitative evaluation of the responses, both number and letter grade was made by the consulting dermatologist based on review of the raw data as well as the graphic representation of the frequency of scores per study day. These data were confirmed by the Medical Officer's review of the primary data. In addition, the Medical Officer confirmed that there were no outliers noticed in the raw data sets for the four test articles and thus the mean data is representative of the group response. Because of the study design, the highest score one would expect is 3+. Outliers beyond this score were not noted in the data since this score automatically led to discontinuation of patching at that site.

The Sano Nicotine Transdermal System elicited an increased score, by frequency of individual scores (1+ to 2+)as well as total score, on study Day 8. Glazing and fissuring became more frequent in study subjects from Day 8 (9 of 39 - 23%) to Day 11 (23 of 39 - 59%) and Day 16 (29 of 34 - 85%). By Day 16, a small number of subjects manifest both definite erythema and glazing and fissuring (7 of 34 - 21%), a clinically significant outcome.

The Habitrol Nicotine Transdermal System overall elicited more frequent scores of 1+ and 2+ after the Day 1 reading than the Sano product. At Day 7 there was a progression to definite erythema (Grade 2+) seen in 19 of 36 (53%). By Day 9, there was a majority reaction of definite erythema (2+) or greater in 27 of 36 (75%). One of these subjects actually had a 3+ reaction. By Day 8, marked glazing with peeling and cracking was noted in 2 and glazing with fissures was seen in 5 subjects. Both

were increased in frequency from the Day 7 measurements (2 - glazing with fissures). Clinically significant reactions were seen in this group after the first 9-11 daily applications. Glazing with peeling and cracking as well as glazing with fissures were noted in most of the subjects after the Day 12 application (18 of 39 - 41%). By Day 16, this reaction was elicited in 25 of 35 subjects (71%) and this observation was considerably higher than the frequency of this reaction seen with the Sano Nicotine Transdermal System (21%).

These data indicate that both the Sano product and Habitrol Nicotine Transdermal System can cause clinically significant irritant reactions. The severity and rapidity with which it was observed to occur was greater with the Habitrol product.

Adverse Events:

Twelve study subjects experienced a total of 24 adverse events during the study. Of these, it was determined that 1 was not related (yeast infection) to study test products and 5 were deemed unlikely to be related (swelling in legs, menstrual cramps, blood clot in legs, tooth pain after eating ice cream, and backache). Patient #110 developed a blood clot in his/her legs and withdrew from the study after 5 days. "Possibly related to drug" adverse reactions included insomnia (1), nausea (1), and headache (5). Itching at patch sites occurred in 7 subjects and was thought to be probably due to the test treatment. The reactions were more frequent at the Nicotine test sites (A-Sano - 5, B-Habitrol - 3) and occurred less frequently at the site of the controls (C-SLS - 1, D-normal saline - 2). Four subjects experienced itching at two sites (A+B - 2, A+D - 1, C+D - 1). Most of the "possible" and "probable" ADE's were short-lived (1 to 2 days). One episode of headache, however, lasted three days and itching at site C and D in one did not resolve for 6 days.

Summary:

A 21-day skin irritation study was done comparing four test articles, Sano Nicotine Transdermal System, Habitrol Nicotine Transdermal System, the RLD, Sodium Lauryl Sulfate (high irritancy control) and Normal Saline (low irritancy control). Both Nicotine Transdermal Systems differed significantly from the high and low irritancy controls in mean score per day, time to patch removal, frequency of grade responses, total and mean irritancy scores as well as time to onset of definite erythema and glazing with fissures. In all the above parameters, the Sano product demonstrated slightly less irritancy than Habitrol product.

Conclusion:

The Sano Nicotine Transdermal System has skin irritation potential which is close to but slightly less than that seen with the reference listed drug, Habitrol Nicotine

Transdermal System.

Recommendation:

The Sano Nicotine Transdermal System should be defined as bioequivalent to Habitrol Nicotine Transdermal System with respect to skin irritation.

4/25/97

Mary M. Fanning, MD, PhD
Associate Director of Medical Affairs

Nicotine Transdermal
7, 14, and 21 mg/day
ANDA #74-612
Reviewer: Moo Park
Filename: 74612ESD.195

Sano Corporation
Pembroke Pines, Florida
Submission Date:
January 20, 1995
April 21, 1995
April 25, 1995

Evaluation of Sano's Electronic Submission Data

I. Objectives

Evaluation of Sano's Electronic Submission Data (ESD) for the *in vivo* bioequivalence study comparing its Nicotine Transdermal, 21 mg/day patch, to Basel Pharmaceuticals' Habitrol^{R}, 21 mg/day patch.

II. Background

Sano along with several other companies volunteered to participate in the pilot program for the OGD Bio-ESD. The objective of the pilot program is to identify problems with the ESD system as early as possible and take necessary actions to correct and improve the system for wider use of the ESD system in the near future by the industry.

The pilot program is going to be evaluated via three-way communication among the participating company, UMAB and OGD. The UMAB staff are more or less looking at the software side which deals with storage and retrieval of the BA/BE. Reviewers in the Division of Bioequivalence are going to evaluate the files submitted in the ESD by sponsors and the output delivered on computer. The UMAB staff and sponsors, upon receiving the comment and recommendation from the reviewer, will make necessary corrections and pass them on to reviewers for further evaluation.

This evaluation is the bio-reviewer's evaluation of data files in ESD format and the output.

III. Evaluation of Data Files

Index of the files (Table 1) submitted in the ESD shows all the information needed to identify a file. There are errors and problems/concerns identified with the files.

(1). The report file (SNO9501.002) is in MS Word. The sponsor was notified to submit the file in WordPerfect. Mr. Holovac is checking whether this can be resolved by adopting different setup for the WordPerfect we have.

(2). Errors detected for each file are listed below:

1. Demographics (CAA)

- No problem.

2. Plasma Pharmacokinetic Parameters for Nicotine (HAA)

   - AUCT was not reported for nicotine. However, the sponsor submitted AUCL (AUC from 0 to last log linear data point). Area based on linear trapezoidal rule (AUCT: AUC from time 0 to time of last non-zero plasma level) should be submitted. The AUCL is handled as an optional data field and will not be used for the 90% CI. AUCT will be used for the 90% CI.

3. Plasma Pharmacokinetic Parameters for Cotinine (HBB)

   - AUCT was reported for cotinine. The AUCT calculation should be based on the linear trapezoidal rule. The 90% CI will be calculated based on the AUCT. The sponsor submitted AUCL (AUC from 0 to last log linear data point) which will be handled as an optional data field.

4. Stability Data (JAA and JBB)

   - %Original field is missing. %Original is simply 100*(found)/(input). The sponsor probably misunderstood or misinterpreted this field.

   - The storage conditions #3 and 4 are inadequate. You can include such conditions as storage under freezing (-20°C), room temperature storage (short-term), autosampler tray, freeze-thaw (3 cycles), etc.

   - Zero time point should be included in the data file.

5. Recovery Data (KAA and KBB)

   - The sponsor changed the names of the two fields, input and found, to extracted and unextracted, respectively. This creates a problem of changing the order of the variables. The sponsor could have explained in the comment section that input is equivalent to unextracted and found is equivalent to extracted for the absolute recovery data. For the relative recovery, input and found should be adequate.

   - %Recovery was not calculated.

6. Quality Control Data (MAA, MBB, MCC and MDD)

- Assay date field is missing.

7. Kel Estimation Data for Cotinine (NBB)

- Error for Subject #20 for the test product. Plasma data show that the last two sampling points have missing data. The data input appears to be erroneous. UMAB's algorithm should be checked since missing values create a problem at the present time.

8. Fraction Absorbed (OAA)

- This is the optional data the sponsor submitted. It is acceptable. The sponsor should explain how this was generated.

IV. Evaluation of Excel Output of the BA/BE Database

The evaluation of the BA/BE database was performed following the General menu and submenus created for the BA/BE database. The content of the output was evaluated as of its appropriateness and correctness when a menu entry was activated.

The study is stored as a workbook and it has three general entries, Submission Info, Study Info and Parent Drug/Metabolites as shown in Table 2. Each entry under General has several submenus as shown in Tables 3-5. Access to any information is achieved through following the General and submenus in a proper sequence.

A. Evaluation of Submission Info: See Table 3.

1. Summary: OK
2. Dissolution data: OK
3. Dissolution summary: OK
4. Assay validation: OK
5. Index: OK

B. Evaluation of Study Info: See Table 4.

1. Study selection: N/A
2. Study facility: OK
3. Study design: OK
4. Treatment info: OK. Strength and dose administered fields need extra attention. Extra field may be needed. Potency and content uniformity data are not transferred.
5. Adverse reaction: OK. No data.
6. Demographic data: OK. Algorithm for IBW and BSA should be given.
7. Parameter calculation: OK. No entry.

8. Subject PD data: OK. No data.
9. Subject demographic data: OK
10. Dropout: OK

C. Parent Drug/Metabolites Info: See Table 5.

For nicotine and cotinine:

1. Summary info: OK
2. Assay validation: OK.
3. Plasma parameters: Problems. AUCT for nicotine was not reported. For cotinine, AUCT and AUCL were reported. The 90% confidence intervals calculated for each PK parameter by the macro is different from the two-one sided t-test based 90% confidence intervals used for regulatory purposes. This will be replaced with a range (minimum and maximum).
4. Urine data: OK. No data.
5. Subject Concentration data: OK
6. Subject urine data: OK. No data.
7. Graph composer: OK. To change to a new graph, old one should always be closed or a new name has to be given to the new graph.
8. Parameter estimation: Malfunction. Algorithms for the missing values should be established. Algorithms for handling subject id number should be developed. Change AUC to AUCT from the selection menu.
9. Highlight Cmax: OK

V. Output/ESD Format To Be Added or Modified

1. Summary table for the standard curve data for the assay validation.
2. Summary table for the quality control sample data for the assay validation.
3. Summary table for the stability data for the assay validation.
4. Summary table for the recovery data for the assay validation.
5. Summary table for the standard curve data for the current study.
6. Summary table for the quality control sample data for the current study.
7. Summary table for the 90% confidence intervals for the PK parameters (sponsor's data). New data file may have to be included for this purpose.
8. Waiver requests for the lower strengths should be listed to complete the overall picture of the submission. New field may have to be added to the ESD template.
9. Full study protocol in WordPerfect should be added in the list of required files.
10. Macro function to view optional data files in table format should be added.

VI. Comments

1. Data files: Twenty-three files were submitted by the sponsor. One file (SNO9501.OAA for fraction absorbed) was optionally submitted by the sponsor.

   There are data submitted in the hard copy which were not submitted in the ESD such as *in vitro* human cadaver skin flux data, carbon monoxide measurement data, skin irritation data, patch skin adherence data, etc. These are all related to the specific requirements for the transdermal dosage form. In general, sponsors should be encouraged to submit all relevant data in ASCII format even though they are not specifically listed in the list of required data files.

   Summary of the evaluation of the data files is listed under II. Evaluation of Data Files. In case of deviations from the original format listed in the template, the sponsor should explain them in the comment section of each data file. Unless it is unavoidable, any deviation is discouraged.

   %Recovery and %Original may have to be explained more clearly in the template. The sponsor used dots (.) instead of numeric data.

   The sponsors should pay attention to the variable names and definitions used in the template. AUCT should not be substituted with AUCL.

   Report file should be submitted in a word processor format which reviewers have access to. Sano's submission in MS Word version 6 was not accessible with the softwares in the OGD. Submission in WordPerfect is recommended.

2. Output: It may be necessary to expand the output to include those suggested in the Output/ESD section. Since sponsors are submitting optional data files, it may be necessary to design a macro function to view those optional data in table format.

VII. Conclusions and Recommendations

1. The ESD will eventually become a powerful tool for reviewing ANDA bio-submissions. The ESD will enable reviewers to complete a thorough review of a bio-study in shorter time. Transferring output to a WordPerfect file was simple and easy task.

2. There are some data files to be corrected by the sponsor. Details are discussed in the main body of this report.

3. There are some additions/modifications to be made by the UMAB in the software. Details are discussed in the main body of this report.

4. The findings in this evaluation will be sent to the sponsor and to the UMAB for corrective measures immediately.

5. The firm submitted two amendments (submission dates: 4/21/95 and 4/25/95) to respond to the deficiencies pointed out in this report which was forwarded to the firm by FAX. The information provided in the amendments were acceptable. These electronic amendments were loaded into the database (N drive).

6. The software-related deficiencies were forwarded to of the UMAB for correction. The macro functions for Excel were updated as a result.

7. No further action is necessary for this electronic submission.

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